IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT Application of
Muller et al.

Group Art Unit: 1618

U.S. App'n Ser. No.: 10/030,417

Examiner: Ebrahim, Nabila G.

Filed: 08/14/2002

Attorney Docket No: 668-59190

For: METHOD FOR CONTROLLED PRODUCTION OF ULTRAFINE MICROPARTICLES AND NANPARTICLES

NOTICE OF APPEAL AND PRE-APPEAL BRIEF

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 2313-1450

Dear Sir:

Applicant respectfully submits that the Examiner omitted essential elements of the claimed invention required for a prima facie rejection of claims 1-17, 20, 24-29, 31-34 and 38-47 under 35 U.S.C. 103(a) as being unpatentable over WO 98/14174 (Desai) in view of U.S. Patent No. 5,858,410 (Muller). Applicant respectfully submits that that the Examiner does not properly distinguish between:

1. Teachings in the prior art on how to produce the particles using a high pressure homogenization medium (organic solvent having less than 50 wt.% water); and
2. Teachings in the prior art on how to use the already produced particles in solvents, such as organic solvents.

Teachings on how to use the already produced particles are very different from teachings on how to produce the partcles in the first place and these teachings are not interchangeable.

The claimed invention requires the use of "an anhydrous or water-reduced dispersion medium containing less than 50 wt. % of water" as a high pressure homogenization medium in a piston-gap homogenizer to produce the particles. [See claims 1, 46 and 47.] The Examiner has not provided a prima facie case of obviousness since both Muller and Desai require the use of water in amounts greater than the claimed less than 50 wt.% as the dispersion medium.

The present Applicant (Rainer Muller) is the same Applicant as in the cited Muller and, thus, Applicant is fully aware of the teachings of Muller. The entire specification of Muller requires the use of a large amount of water (about 80 to 99 % of water) as the high pressure medium in order to create cavitation and produce the particles. Muller teaches that the "dispersion principle is cavitation." See column 4, lines 6-7. Cavitation by definition requires a large amount water and, thus, Muller teaches against using less water. At column 5, lines 27-28, Muller teaches that "Suspensions were prepared with a drug, which was ground in an air jet, in an aqueous surfactant solution." [Emphasis added.] The specification of Muller in fact teaches that the high pressure dispersion medium is water or an aqueous medium containing about 80 to 99 % of water. There is no disclosure of using a non-aqueous high pressure homogenization medium or of a water reduced (less than about 50% of water) high pressure homogenization medium.

In some examples of Muller, glycerol is used as an emulsion stabilizer. However, glycerol cannot be considered as an organic solvent medium for high pressure homogenization and its content in all cases is below 16.7%. All other components used are solids (such as mannitol and phospholipon). Mannitol is introduced in form of an aqueous solution. Thus, there is no organic solvent at all.

Applicant respectfully submits that the Examiner's statement in the first paragraph of page 4 of the Final Office Action, in regards to claim 38 is incorrect. The disclosure of a feature of an active compound (drug) of being insoluble, only sparingly soluble or moderately soluble in organic solvents does not disclose that the organic solvents are used as the dispersion medium to produce the particles. Indeed, the Examiner has not, and cannot, cite any language in the specification of Muller that teaches to use less than 50 wt.% water in the dispersion medium.

Applicant respectfully submits that the Examiner misinterprets the Abstract of Muller at page 6, first paragraph of the Final Office Action, that "a step of further modifying a particle can still be considered as a method of producing a particle." The Abstract of Muller merely discloses that the drug carrier comprises particles of a pure active compound, which is insoluble or sparingly soluble in organic solvents. This language absolutely does not teach or suggest that organic solvents, which

contain less than 50 wt.% water, should be used as a dispersion medium in a piston-gap homogenizer. The Examiner has not, and cannot, cite any language in the specification that teaches to use less than 50 wt.% water in the dispersion medium. Dispersing particles produced by the water-based high pressure homogenization process of Muller thereafter in an organic solvent for further purposes cannot be read as a production of such particles in a dispersion medium consisting of the organic solvent.

Desai does not provide the deficiencies of Muller. All of Desai's Examples use a dispersion medium of which 85% or more is water. This is by way of using a 1% (w/v) serum albumin solution in an amount resulting in such high water contents.

Applicant respectfully submits that the Examiner's assertion at the bottom of page 7 of the Final Office Action, that "Desai did not disclose the use of water in the process of making the particles in different embodiments (see for example 1) which teaches 30 mg paclitaxel disssolved in 3.0 ml human serum albumin soltion (1 % w/v)", has no factual basis. Example 1 of Desai on page 33 clearly discloses that 30 mg paclitaxel is dissolved in 3.0 ml of methylene chloride, which solution is added 27.0 ml of a solution of human serum albumin having a concentration of 1% w/v. This mixture is finally high pressure homogenized using an Avestin homogenizer. Thus, the major component of the high pressure homogenization medium is indeed water (90%). Moreover, the use of serum albumin as such is not the critical point. The critical point is that Desai uses it in form of a 1% w/v solution, and thus always introduces a high amount of water into the dispersion medium prior to the homogenization. These teachings in Desai cannot be ignored. The Examiner's statement at the top of page 9 of the Office Action that, "Further, the serum albumin as a solution is only disclosed in examples 22 and 23" is incorrect. A serum albumin solution is used in all examples of Desai. See e.g. Example 1 where it is stated that 27.0 ml of human serum albumin solution (1 % w/v) is added. A corresponding situation is explicitly mentioned in Desai's Examples 2, 4, 6, 7, 9, 10, 11, 12, 22, and 23.

Furthermore, Desai teaches away from using higher amounts of organic solvents. As can be seen from Example 7 of Desai at page 38, an alteration of the

organic phase fraction showed that increasing the phase fraction led to a significant increase in particle size. Even a shift from 2% to 3% to 4% resulted in a particle size increase from 150 nm to 200 nm to 250 nm, which teaches to those skilled in the art that a further shift to an organic phase fraction of more than 50% would be expected to result in particle sizes well above the limit of the claimed invention. Thus, there is the clear teaching in Desai not to use dispersion media having a low (less than 85%) or even no water content.

It is general knowledge in the art to use water as dispersion medium for piston-gap homogenizers because only water has been considered to provide a sufficient amount of cavitation (Muller) effect required for piston-gap homogenizers to function. Consequently, use of a piston-gap homogenizer in anhydrous or considerably water reduced media (such as below 85% of water) was not known prior to the present invention. Thus, it is not a simple matter to change from one homogenizing device to another, such as from Desai's Avestin homogenizer to the claimed piston-gap homogenizer, without considering also the other requirements for such devices, in particular the homogenization medium.

Even if a person of ordinary skill in the art would have considered to use a piston-gap homogenizer with Desai's method, such a person would have seen the requirement to use mainly water as dispersion medium with an amount of 85% of water or higher, and therefore would not have considered with any expectance of success a reduction of the water content to below 50%. Thus, the combination of Desai and Muller would not have resulted in the claimed invention using an anhydrous or water-reduced (less than 50%) dispersion medium, but only in the use of a medium having a content of at least 85% of water. There is no disclosure in any of the cited documents which might invite a person of average skill in the art to modify their teachings in such a way that the presently claimed process would be obtained.

Regarding the Examiner's statement at the top of page 12 of the Final Office Action, it should be noted that the teachings of Muller with respect to cavitation and shear forces has to be divided. The cavitation effect is related to the use of a piston-gap homogenizer, while the shear and impact forces are related to other devices

such a microfluidizer or nanojet using the jet stream principle. See column 4, lines 16-21, and column 5, lines 6-7, respectively. Since the claimed method requires the use of a piston-gap homogenizer, the mention of shear and impact forces related to other devices in Muller are of no relevance.

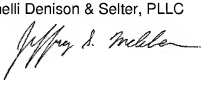
The primary goal of the present invention is to provide an effective yet gentle process for the preparation of hydrolysis and temperature sensitive micro- and nanoparticles, and stable dispersions thereof, with high chemical stability of active ingredients and increased dispersity of suspensions with prevented aggregation. The claimed invention allows the active ingredients to be filled into capsules without need for intermediate process steps of removal and addition of media, and to process the particles obtained to tablets and pellets. These goals are met by way of a unique and surprising combination of features:

- an anhydrous or considerably water reduced (less than 50% water) dispersion medium instead of mainly water, and in combination
- a piston-gap homogenizer instead of other homogenization devises such as a micro-fluidizer.

None of the prior art can realize these benefits since none teach or disclose the use of an anhydrous or considerably water reduced (less than 50% water) dispersion medium and the use of a piston-gap homogenizer.

In view of the many differences between the claimed invention and the theoretical combination of Desai and Muller, and the unexpected advantages of the claimed invention, withdrawal of the Section 103 rejection is respectfully requested.

Respectfully submitted,
Manelli Denison & Selter, PLLC



By

Jeffrey S. Melcher
Reg. No.: 35,950
Tel. No.: 202.261.1045
Fax. No.: 202.887.0336
Customer No. 90042